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(54) Title: STABLE PHARMACEUTICAL SOLUTION FORMULATIONS FOR PRESSURISED METERED DOSE INHALERS

(57) Abstract: An aerosol solution composition for use in an aerosol inhaler comprises an active material, a propellant containing a hydrofluoroalkane, a cosolvent and optionally a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler. The composition is stabilized by using a small amount of mineral acid and a suitable can having part or all of its internal metallic surfaces made of stainless steel, anodized aluminium or lined with an inert organic coating.

STABLE PHARMACEUTICAL SOLUTION FORMULATIONS FOR PRESSURISED METERED DOSE INHALERS.

The invention relates to stable pharmaceutical solution to be used with pressurised metered dose inhalers (MDIs) suitable for aerosol administration. In particular, the invention relates to solution to be used with pressurised metered dose inhalers (MDIs), suitable for aerosol administration containing β_2-agonists and stable at room temperature for a pharmaceutically acceptable shelf-life.

Pressurised metered dose inhalers are well known devices for administering pharmaceutical products to the respiratory tract by inhalation.

Drugs commonly delivered by inhalation include bronchodilators such as β_2-agonists and anticholinergics, corticosteroids, anti-leukotrienes, anti-allergics and other materials that may be efficiently administered by inhalation, thus increasing the therapeutic index and reducing side effects of the active material.

MDI uses a propellant to expel droplets containing the pharmaceutical product to the respiratory tract as an aerosol. Formulations for aerosol administration *via* MDIs can be solutions or suspensions. Solution formulations offer the advantage of being homogeneous with the active ingredient and excipients completely dissolved in the propellant vehicle or its mixture with suitable co-solvents such as ethanol. Solution formulations also obviate physical stability problems associated with suspension formulations so assuring more consistent uniform dosage administration.

For many years the preferred propellants used in aerosols for pharmaceutical use have been a group of chlorofluorocarbons which are commonly called Freons or CFCs, such as CCl_3F (Freon 11 or CFC-11), CCl_2F_2 (Freon 12 or CFC-12), and $CClF_2$-$CClF_2$ (Freon 114 or CFC-114).

Recently, the chlorofluorocarbon (CFC) propellants such as Freon 11 and Freon 12 have been implicated in the destruction of the ozone layer and their production is being phased out.

Hydrofluoroalkanes [(HFAs) known also as hydro-fluoro-carbons (HFCs)] contain no chlorine and are considered less destructive to ozone and these are

proposed as substitutes for CFCs.

HFAs and in particular 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) have been acknowledged to be the best candidates for non-CFC propellants and a number of medicinal aerosol formulations using such HFA propellant systems have been disclosed.

Due to the higher polarity of the HFA propellants, in particular of HFA 134a (dielectric constant $D > 9.5$), with respect to CFC vehicles ($D < 2.3$), HFA solution formulations may suffer to a greater extent of chemical stability problems with respect to the corresponding CFC formulations.

Preparation of stable HFA solution formulations is even more critical when bronchodilator β_2-agonists belonging to the class of the phenylalkylamino derivatives are concerned; said drugs, like formoterol and salbutamol (albuterol), may suffer of inherent chemical stability problems due to their susceptibility to oxidative conditions; moreover, in the view of the presence of some functional groups like formamide, a higher polarity of the vehicle may accelerate the rate of solvolysis reactions.

As far as formoterol, the currently marketed CFC solution formulation (Foradil®) exhibits indeed a limited shelf life, i.e. 12 months at refrigerator temperature, 4± 2°C, and only 3 month at room temperature.

As far as salbutamol, no formulation as HFA solution for aerosol administration is currently on the market.

In consideration of the problems outlined, it would be highly advantageous to provide a formulation in the form of HFA solution to be administered by MDI's aimed at providing pharmaceutical doses of β_2-agonists characterised by adequate shelf-life.

OBJECT OF THE INVENTION

It is an object of the invention to provide a formulation in the form of HFA solution to be administered by MDI's for providing pharmaceutical doses of β_2-agonists into the low respiratory tract of patients suffering of pulmonary diseases such as asthma, characterised by adequate shelf-life. In particular, it is an object of the invention to provide a formulation in the form of HFA solution to be administered by MDI's for providing pharmaceutical doses of

formoterol with a greater shelf-life of that of the formulation currently on the market.

According to the invention there is provided a pharmaceutical composition comprising a β_2-agonist belonging to the class of phenylalkylamino derivatives in a solution of a liquefied HFA propellant, a co-solvent selected from pharmaceutically acceptable alcohols, solution whose apparent pH has been adjusted to between 2.5 and 5.0 by addition of small amounts of a mineral acid. The composition of the invention shall be contained in a pressurised MDI having part or all of its internal metallic surfaces made of stainless steel, anodised aluminium or lined with an inert organic coating.

In fact, it has been found that, in the case of certain active ingredients such as β_2-agonists, their chemical stability in HFA solution formulations could be dramatically improved by a proper and combined selection of the kind of cans as well as the apparent pH range. The attribution 'apparent' is used as pH is indeed characteristic of aqueous liquids where water is the dominant component (Mole Fraction > 0.95). In relatively aprotic solvents such as the HFA-ethanol vehicles used in these studies, protons are non-hydrated; their activity coefficients differ significantly from those in aqueous solution. Although the Nernst equation with respect to EMF applies and the pH-meter glass electrode system will generate a variable milli-volt output according to proton concentration and vehicle polarity, the "pH" meter reading is not a true pH value. The meter reading represents an apparent pH or acidity function (pH').

When the active ingredient was titrated with a strong acid in a model vehicle system commercially available (HFA 43-10MEE, Vertrel XF, Dupont), the pH' profile exhibits a shallow negative to about pH' = 5.5; thereafter the acidity function drops abruptly. Surprisingly the corresponding HFA formulations turned out to much more stable below pH' 5.5.

On the other hand, the use of inert containers allows to avoid the leaching of metal ions or alkali as a consequence of the action of the acid contained in the formulation onto the inner walls of the cans. Metal ions such Al^{3+} or alkali respectively deriving from the conventional aluminium or glass cans could in

turn catalyse radical oxidative or other chemical reactions of the active ingredient which give rise to the formation of degradation products.

According to a particular embodiment of the invention there is also provided a pharmaceutical composition further containing a low volatility component in such a way as to, besides increasing the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler as explained in the following, further improving the stability of the formulation. In fact, the addition of a low volatility component with a reduced polarity with respect to the co-solvent such as an ester may allow either to reduce the amount of acid to be added for adjusting the pH and diminish the polarity of the medium so limiting the possible uptake of environmental water. In the case of active ingredients such as formoterol, it is well known that the latter (e.g. humidity) could be detrimental to the stability of the active ingredient during storage. Accordingly, there is also provided a pressurised MDI for administering pharmaceutical doses consisting of an anodised aluminium container filled with a pharmaceutical composition consisting of a formoterol fumarate solution in HFA 134a as a propellant in turn containing 12% *w/w* ethanol as a co-solvent and 1.0% *w/w* isopropyl myristate as a low volatility component, the apparent pH of said solution having been adjusted to between 3.0 and 3.5 by addition of small amounts of hydrochloric acid. The expression '% w/w' means the weight percentage of the component in respect to the total weight of the composition.

The shelf-life of the formulation put in the device of the invention could be predicted to be greater than two years at the refrigerator temperature (4-10°C) and three months at room temperature.

A person sufficiently skilled in the art can easily apply the teaching of the present invention to the preparation of HFA solution formulations containing other active ingredients bearing functional groups, sensitive to hydrolytic and/or oxidative reactions, such as formamide and cathecol respectively.

WO 97/47286, EP 513127, EP 504112, WO 93/11747, WO 94/21228, WO 94/21229, WO 96/18384, WO 96/19198, WO 96/19968, WO 98/05302, WO 98/34595 and WO 00/07567 disclose HFA formulations in the form of suspensions in which β_2-agonists such formoterol and salbutamol are either

exemplified and/or claimed.

WO 99/65464 refers to HFA formulations containg two or more active ingredients in which at least one is in suspension. The preferred formulations comprises salbutamol sulphate in suspension.

In WO 98/34596, the applicant described solution compositions for use in an aerosol inhaler, comprising an active material, a propellant containing a hydrofluoroalkane (HFA), a cosolvent and further comprising a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler. Said application does not address the technical problem of the chemical stability of the active ingredient but it rather concern the drug delivery to lungs.

In the international application n° PCT/EP99/09002 filed on 23/11/99 the applicant disclosed pressurised MDI's for dispensing solution of an active ingredient in a hydrofluorocarbon propellant, a co-solvent and optionally a low-volatility component characterized in that part or all of the internal surfaces of said inhalers consist of stainless steel, anodised aluminium or are lined with an inert organic coating. The examples are referred only to steroids and anticholinergic agents and no acidified solutions are envisioned. As demonstrated in the example 1 of the present application, the use of coated containers, even in the presence of an organic acid, is not sufficient for providing stable solution formulations of a phenylalkylamino derivative such as salbutamol.

EP 673240 proposes the use of acids as stabilisers preventing the chemical degradation of the active ingredient in aerosol solution formulations comprising HFAs. Most examples relate to ipratropium bromide, an anticholinergic drug and only an example is presented for a β_2-agonist, i.e. fenoterol. No exemplary formulations for salbutamol are provided. It is evident from the data reported in the example 1 of the present application, that salbutamol cannot be stabilised at all by addition of organic acids even when stored in coated cans. Furthermore, apart from ipratropium bromide, in EP 673240 no guidance is given with respect to the amount of acid which has to be added in order to stabilise the medicaments without compromising the stability of the whole composition in the can. The only hint can be found on

page 5, lines 15 to 16 which says that an amount of inorganic acid should be added to obtain a pH value from 1 to 7, so a very broad and generic range.

WO 98/34596 refers to solution formulations containing a propellant and a physiologically acceptable polymer which could help the solubilisation and the stability as well of the active ingredients.

WO 00/06121 refers to propellant mixtures for aerosol dinitrogen monoxide and a hydrofluoroalkane in the preparation of suspension and solution aerosols. The use of dinitrogen monoxide may improve the stability at storage of oxidation-sensitive active ingredients. As far as β_2-agonist such levosalbutamol sulphate, formoterol fumarate and salmeterol xinafoate, only examples referred to suspensions are reported.

WO 99/65460 claims pressurised MDI's containing stable formulations of a β-agonist drug in suspension or solution. Examples refer to solutions of formoterol fumarate containing an HFA propellant and ethanol as co-solvent, filled in conventional aluminium or plastic coated glass cans.

Samples stored under accelerated conditions (40°C, 75% relative humidity) for a very short period, one month, exhibited about 10% loss of drug. According to pharmaceutical guidelines on stability, loss of 10% of active ingredient does not meet the criteria of acceptance. Moreover, as it is evident from the data reported in Example 2 of the present application, following the teaching of WO 99/65460 stable formoterol solution formulations cannot be provided. Applicant has indeed demonstrated that the presence of low-volatility components does not substantially affect the chemical stability of the compositions. In some cases, they could even improve it.

According to a further aspect of the invention there is provided a method of filling an aerosol inhaler with a composition of the invention, the method comprising:

(a) Preparation of a solution of one or more active ingredients in one or more co-solvents optionally containing an appropriate amount of a low volatility component.

(b) Filling of the device with said solution.

(c) Adding a pre-determined amount of a strong mineral acid.

(d) Adding a propellant containing a hydrofluoroalkane (HFA).

(e) Crimping with valves and gassing.

Active ingredients which may be used in the aerosol compositions of the invention are short- and long-acting β_2-adrenergic agonists such as salbutamol, formoterol, salmeterol, TA 2005, salt thereof and their combinations with steroids such as beclomethasone dipropionate, fluticasone propionate, budesonide and its 22R-epimer. Other amino type drugs bearing functional groups sensitive to oxidative and/or hydrolytic reactions can be advantageously used.

Preferably the composition will be contained in anodised aluminium cans. Suitable coated device can also be used.

Metering valves fitted with gaskets made of chloroprene-based rubbers can preferably be used to reduce the ingress of moisture which, as previously mentioned, can adversely affect the stability of the drug during storage. Optionally, further protection can be achieved by packaging the product in a sealed aluminium pouch.

The hydrofluorocarbon propellant is preferably selected from the group of HFA 134a, HFA 227 and mixtures thereof.

The co-solvent is usually an alcohol, preferably ethanol.

The low volatility component, when present, has a vapour pressure at 25°C lower than 0.1 kPa, preferably lower than 0.05 kPa. It could be selected from the group of glycols, particularly propylene glycol, polyethylene glycol and glycerol, esters for example ascorbyl palmitate, isopropyl myristate and tocopherol esters.

The compositions of the invention may contain from 0.2 to 10% w/w of said low volatility component, preferably between 0.5 and 2.0% w/w.

Propylene glycol, polyethylene glycol, glycerol and esters are the preferred low-volatility components.

The function of the low volatility component is to modulate the MMAD of the aerosol particles and preferably to further improve the stability of the formulation. With respect to the latter aspect, particularly preferred is the use of isopropyl myristate.

The apparent pH range is advantageously comprised between 2.5 and 5.0, preferably between 3.0 and 4.5, even more preferably between 3.0 and 3.5. Strong mineral acids such as hydrochloric, nitric, phosphoric are preferably used to adjust the apparent pH.

The amount of acid to be added to reach the desired apparent pH will be pre-determined in the model vehicle reported before and it will depend on the type and concentration of the active ingredient. In the case of formoterol, an amount comprised between 3 and 3.5 µl of 1.0 M hydrochloric acid should be preferably added.

The following examples further illustrate the invention.

Example 1

Stability of salbutamol (100 µg/dose)-HFA 134a solution as such and in the presence of different organic acids.

Compositions containing 24 mg of salbutamol (100 µg/dose), 10-20% (w/w) ethanol in HFA 134a put in 12 ml epoxy phenol resin lacquered cans, with or without addition of different organic acids, were stored at 40- 50°C.

The results in term of stability expressed as percentage of remaining drug determined by HPLC, are reported in Table 1.

Table 1

Acid	% SALBUTAMOL t = 42 days	t= 1.5 months at 4°C
None	69%	-
Oleic	69-70%	-
Xinafoic	70%	-
Citric (0.41 w/w)	-	40.0
Citric (0.02 w/w)	-	55.1
30% Acetic acid (0.4% w/w)	-	49.6
30% Acetic acid (0.14% w/w)	-	73.8

The results show that the addition of organic acids does not improve the stability of salbutamol even when coated cans are used.

Example 2

Stability of formoterol (12µg/100µl) -HFA 134a compositions in epoxy-phenol resin lacquered cans.

Solution formulations were prepared by dissolving 1.44 mg of formoterol fumarate in HFA 134a in turn containing 15% w/w ethanol and 1.3% w/w glycerol. pMDIs were stored upright over the range 4-50°C for up to 28 days. Formoterol content was determined by HPLC and the percent residual concentrations calculated relative to the 12µg/shot nominal dose. The percent residual formoterol concentration is reported in Table 2. Derived Arrhenius parameters were used to estimate rate constants at ambient temperature (18-25°) and solutions stored in a domestic refrigerator (4-10°); these rate constants were used to calculate predicted shelf-life for 5% and 10% degradation of formoterol.(Table 3).

The calculated shelf-life data in Table 3 indicates that formoterol is not stable in this HFA 134a-ethanol-glycerol vehicle.

Table 2: Degradation Rate Data for Formoterol-HFA 134a pMDI Solutions (12µg/100µl)
Vehicle: HFA 134a with 1.3% w/w Glycerol, 15.0% w/w Ethanol
Epoxy-phenol lacquered cans stored upright

Time (days)	Percent Residual Conc. Formoterol				
	50°C	43°C	40°C	25°C	4°C
Initial	99.7	99.7	99.7	99.7	99.7
2	92.5	-	-	-	-
4	87.2	89.4	-	-	-
6	80.6	-	-	-	-
7	-	-	89.0	-	-
10	74.9	-	-	-	-
12	72.1	79.4	-	-	-
14	67.0	-	81.7	92.0	-
16	64.4	75.7	-	-	-
18	59.5	-	-	-	-
20	59.5	74.5	-	-	-
24	54.6	68.6	-	-	-
28	47.2	63.3	71.3	86.6	96.7
r	0.995	0.989	0.993	0.997	-
Rate Constant ($day^{-1} \times 10^2$)	2.53	1.49	1.17	0.51	0.11
Arrhenius Plot Parameters: $K = Ae^{E/RT}$					
$A = 2.28 \times 10^6\ day^{-1}$: $E = 49.4\ kJ\ mol^{-1}$; $r = 0.9985$					

Table 3: Predicted Shelf Life Data for Formoterol-HFA 134a pMDI Solutions (12μg/100μl)
Vehicle: HFA 134a with 1.3% w/w Glycerol, 15% w/w Ethanol
Epoxy-phenol lacquered cans stored upright

Temperature	Rate Constant ($day^{-1} \times 10^3$)	Shelf-Life (days)	
		$t_{10\%}$	$t_{5\%}$
4°C	1.10	95	47
10°C	1.74	60	29
20°C	3.51	30	15
25°C	4.93	21	10

Example 3

Effect of hydrochloric acid on solution pH' (acidity function)

(a)1.0 M hydrochloric acid was added incrementally to 50ml of HFA 43-10MEE (Vertrel XF) containing 20% w/w ethanol and pH' measured after each aliquot of acid. Figure 1 shows the resultant titration curve normalised to the usual fill volume of a pMDI can (12ml). The pH' profile exhibits a shallow negative slope to about pH'=5.5; thereafter the acidity function drops abruptly.

(b) Experiment (a) was repeated with formoterol formulations containing a lower concentration of ethanol (12% w/w) and with the addition of 1.0% isopropyl myristate. The resultant pH profile, for replicate bulk solutions, shown in Figure 2 is similar in shape with the abrupt fall in pH' per unit increment of acid again commencing at about pH' = 5.5. However, only about half the acid is required to achieve the same reduction in pH'. This is largely due to the reduction in ethanol content; Figure 2 also shows similarity in the profiles obtained with and without isopropyl myristate.

Example 4

Effect of pH' on Stability of Formoterol Solutions in HFA 43-10MEE containing 20% w/w ethanol

Aliquots of 1.0 M hydrochloric acid were added to 12ml of formoterol solution in glass vials. After measurement of pH, valves were crimped on and the vials stored upright at 50°C. Vial samples containing different

concentrations of acid were assayed for residual formoterol after 10 and 20 days storage. The pH' of a third vial was determined after 40 days storage. Results are shown in Table 4. Table 4 shows changes in pH on storage; this is probably largely associated with leaching of alkali from the soft glass of the vials. However, overall consideration of the pH' and formoterol content data implies that the stability of a solution formulation of the drug in HFA can be improved by the addition of mineral acid to provide a formulation with pH' between 2.5-5.0.

Table 4: pH' and Formoterol Content of Formoterol-Vertrel XF/HFA Solutions (12μg/100μl)
Vehicle: Vertrel XF/HFA with 20% Ethanol and Hydrochloric Acid
St Gobain glass vials stored upright

Acidity Function (Ph')		**Percent Residual Conc. Formoterol**		
Initial	**40 days**	**Initial**	**10 days**	**20 days**
1.8	2.8	100	4.8	Nil
2.1	4.4	100	75.1	70.7
2.6	4.2	100	97.2	86.7
3.3	4.2	100	97.1	89.9
5.6	6.6	100	95.8	92.1
7.4	6.7	100	85.4	67.2

Example 5

Stability of acidified formoterol–HFA 134a solutions in anodised cans

Formoterol formulations (12μg/100μl) were prepared by dissolving 1.44 mg of formoterol fumarate in HFA 134a containing 12% *w/w* ethanol with and without 1.0% *w/w* isopropyl myristate. The latter was included as a non-volatile excipient with the potential for increasing MMAD if so desired. It also improves the solubility of formoterol in the vehicle and reduces polarity of the vehicle compared to the addition of glycerol.

pMDI cans containing 3.1-3.4μl 1.0 M hydrochloric acid were set down on storage, upright and inverted, at 4°C to 50°C and samples taken for analysis of formoterol content at appropriate intervals.

Stability data obtained after 70 days of storage are given in Table 5.

A matrix of formulations containing 1.44 mg (12μg/100μl) formoterol fumarate were prepared in HFA 134a containing 12.0% *w/w* ethanol with or without 1.0% *w/w* isopropyl myristate as non-volatile excipient. Aliquots of drug concentrate were transferred to anodised cans and 3.15-3.35μl of 1.0M hydrochloric acid added prior to crimping with 50μl valves and gassing between 22 and 28 replicates at each acid strength were prepared.

To determine residual formoterol, 30 x 50μl shots were discharges into DUSA tubes. The acid range selected was anticipated to give pH' values of 3.0-3.5 and to determine the formulation sensitivity to small changes in acid concentration. Cans were placed on stored upright and inverted (valve up and down respectively) at 25-50°C.

Table 5 shows the results obtained at 40° and 50° after 11-40 day's storage. Each value (expressed as per cent nominal drug concentration) is obtained from a different can.

Initial values were obtained for two cans of each acid strength. Inspection of the data shows all assay values to within the reproducibility of the HPLC assay and independent of acid strength. A similar conclusion was drawn for the storage time point replicates, i.e., independent of acid strength (3.2-3.3μl) or whether cans were stored upright or inverted. Consequently for kinetics calculation the mean value for initial (n=10) and subsequent time points (n=6) was used.

In Table 6 are reported the Arrhenius parameters together with estimated shelf lives at 4, 10 and 25°C. The $t_{5\%}$ is predicted to be greater than 3 months at ambient temperature and approximately 2 years at 4°C.

Table 5: Stability Data for Formoterol Fumarate Solutions (12µg/100µl) in HFA
134a containing 12.0% Ethanol ± 1.0% Isoproyl Myristate
(values are expressed as percent nominal)
Anodised cans fitted with 50µl valves/30 doses collected per can
Different cans assessed at each condition
Cans stored upright (* inverted)

1.0M HCl µl per Can	STORAGE CONDITION/No isopropyl myristate							
	Initial		40°C; 40 days		50°C; 11 days		50°C; 33 days	
	1st Can	2nd Can	1st Can	2nd Can	1st Can	2nd Can	1st Can	2nd Can
3.15	99.8	99.6	-	-	-	-	-	-
3.20	100.8	99.7	96.0	93.2*	96.7	96.5	88.5	89.9*
3.25	97.9	98.8	93.9	94.3*	96.4	96.5	92.2	91.5*
3.30	97.3	98.9	93.7	93.7*	97.0	89.1	90.9	92.8*
3.35	100.0	98.3	-	-	-	-	-	-
Mean	99.1		94.1		95.4		91.0	
C.V.	1.1%		1.0%		3.2%		1.8%	

1.0M Hcl µl per Can	STORAGE CONDITION/1.0% isopropyl myristate							
	Initial		40°C; 33days		50°C; 11 days		50°C; 31 days	
	1st Can	2nd Can	1st Can	2nd Can	1st Can	2nd Can	1st Can	2nd Can
3.15	101.1	99.3	-	-	-	-	-	-
3.20	97.0	100.2	94.4	93.2*	93.8	93.6	90.6	92.7*
3.25	101.4	100.2	98.6	95.0*	96.1	95.9	91.6	89.7*
3.30	99.9	100.8	92.8	95.3*	95.6	95.7	90.0	89.6*
3.35	99.2	97.2	-	-	-	-	-	-
Mean	99.6		94.9		95.1		90.7	
C.V.	1.5%		2.2%		1.2%		1.4%	

Table 6: Shelf Life Prediction for Acidified Formoterol Fumarate Solution (12μg/100μl) in HFA 134a containing 12% w/w Ethanol ± 1.0% w/w isopropyl Myristate (IPM)

Anodised aluminium cans

TIME (days)	FORMOTEROL FUMARATE (percent nominal)			
			40°C	
	Nil IPM	1% IPM	Nil IPM	1% IPM
0	99.1	99.6	99.1	99.6
11	95.4	95.1	-	-
31	-	90.7	-	-
33	91.0	-	-	94.9
40	-	-	94.1	-
Rate Const. ($day^{-1} \times 10^3$)	2.52	2.94	1.29	1.46

Arrhenius Parameters	Frequency Factor (day^{-1})	Activation Energy (kJ mol^{-1})
Nil IPM	3.19×10^6	56.3
1% w/w IPM	9.63×10^6	58.9

TEMPERATURE	Nil IPM			1.0% w/w IPM		
	Rate Const. (day^{-1})	$t_{10\%}$ (days)	$t_{5\%}$ (days)	Rate Const. (day^{-1})	$t_{10\%}$ (days)	$t_{5\%}$ (days)
4°C	7.8×10^{-5}	1344	657	7.8×10^{-5}	1360	664
10°C	1.3×10^{-4}	802	392	1.3×10^{-4}	789	386
25°C	4.4×10^{-4}	240	117	4.4×10^{-4}	225	110

CLAIMS

1. An aerosol composition which comprises an amino type drug bearing a functional group sensitive to oxidative and/or hydrolytic reaction in a solution of a liquefied HFA propellant, a co-solvent selected from pharmaceutically acceptable alcohols, wherein the pH of the solution has been adjusted to between 2.5 and 5.0 by addition of small amounts of a mineral acid such as hydrochloric, nitric or phosphoric acid.

2. A composition according to claim 1, wherein the pH of the solution has been adjusted between 3.0 and 3.5.

3. A composition according to claims 1-2, wherein the solution includes a low volatility component with a vapour pressure at 25°C not more than 0.1 kPa, preferably not more than 0.05 kPa.

4. A composition according to any preceding claim, wherein the solution includes at least 0.2% by weight of the low volatility component and not more than 10% by weight.

5. A composition according to claims 1-4, wherein the cosolvent is an alcohol, preferably ethanol.

6. A composition according to any preceding claim, wherein the low volatility component is selected from a glycol or an ester.

7. A composition according to claim 6, wherein the low volatility component is isopropyl myristate.

8. A composition according to any preceding claim, wherein the propellant includes one or more HFAs selected from the group comprising HFA 134a and HFA 227.

9. A composition according to any preceding claim wherein the active ingredient is a β_2-agonist selected from salbutamol, formoterol, salmeterol and TA-2005, salts thereof or their combination with steroid such as beclomethasone dipropionate, fluticasone propionate, budesonide and its 22R-epimer.

10. A pressurised metered dose inhaler for aerosol administration consisting of a container having part or all of its internal metallic surfaces made of stainless steel, anodised aluminium or lined with an

inert organic coating, containing a composition according to claims 1-9.

11. A method of filling the inhaler of claim 10, the method comprising:

(a) preparation of a solution of one or more active ingredients in one or more co-solvents optionally containing an appropriate amount of a low volatility component;

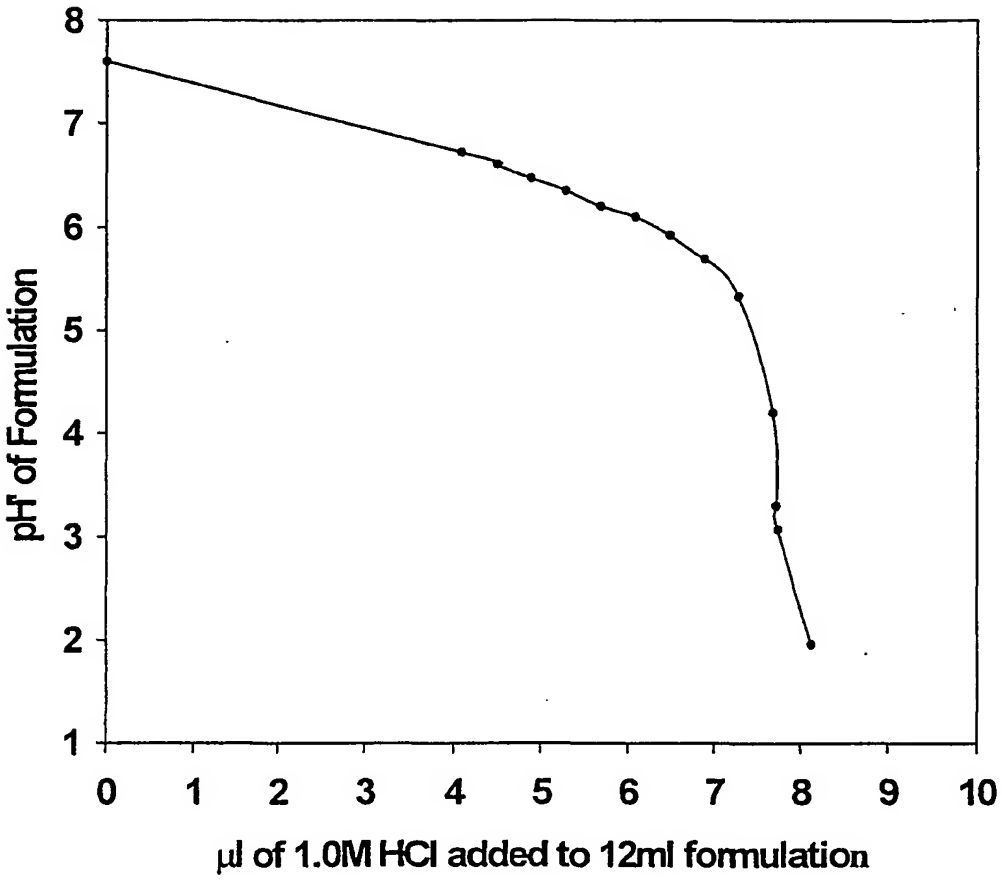
(b) filling the device with said solution ;

(c) adding a pre-determined amount of a strong mineral acid ;

(d) adding a propellant containing a hydrofluoroalkane (HFA);

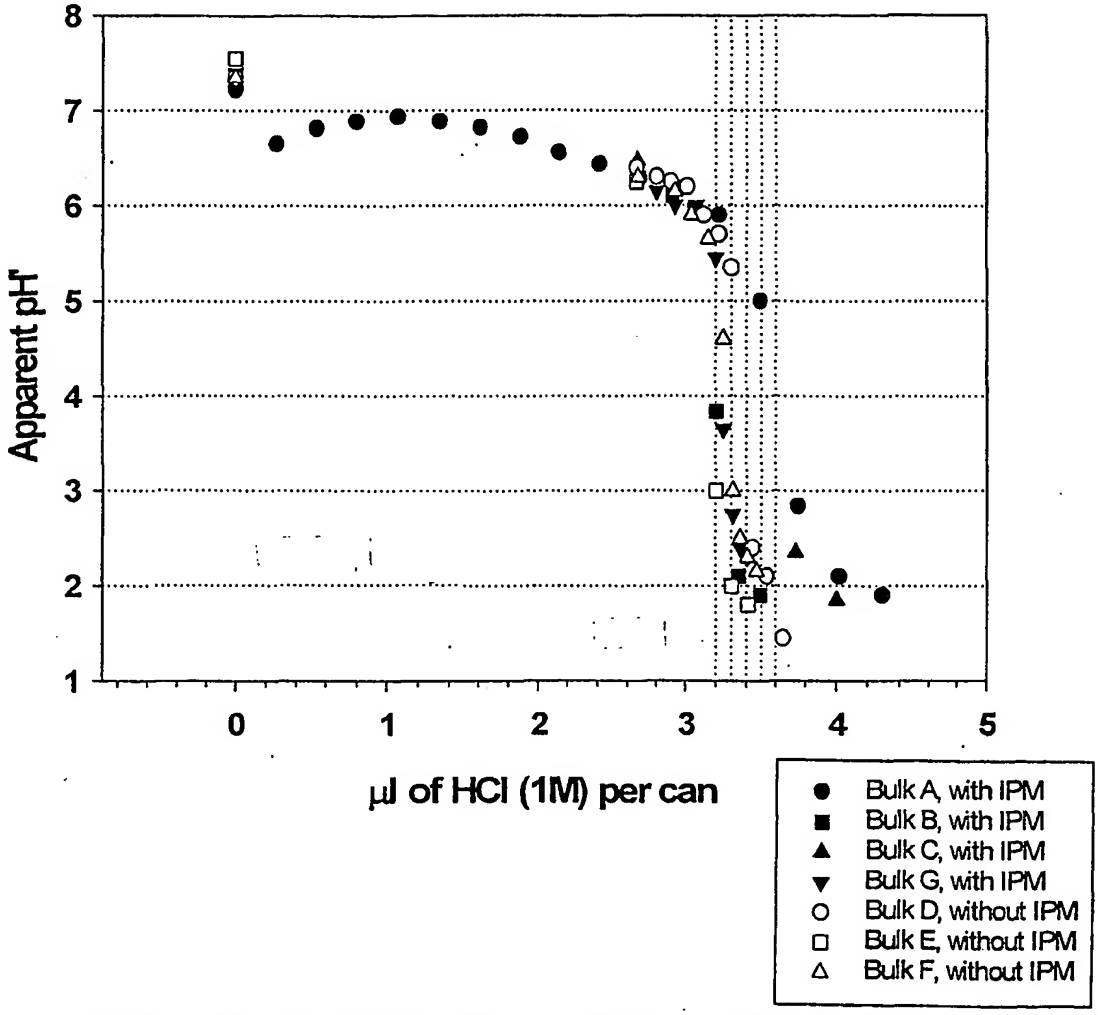
(e) crimping with valves and gassing.

Fig. 1



Effect of hydrochloric acid on Acidity Function (pH') of Formoterol Fumarate Solution (12µg/100µl) in Vertrel XF/HFA containing 20% w/w Ethanol.

2/2
Fig. 2



Effect of hydrochloric Acid on Acidity Function (pH') of Formoterol Fumarate Solution (12µg/100µl) in Vertrel XF/HFA containing 12% w/w Ethanol

(IPM = Isopropyl Myristate)

INTERNATIONAL SEARCH REPORT

Int. ›nal Application No
PCT/EP 00/04635

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/12 B65D83/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K B65D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 13262 A (JAGER PAUL D ;KONTNY MARK J (US); NAGEL JURGEN H (DE)) 23 June 1994 (1994-06-23) cited in the application page 4, paragraph 4 -page 5, paragraph 1 page 4, last paragraph -page 6, paragraph 2 page 9, last paragraph -page 10, last paragraph page 12, last paragraph -page 15, last paragraph page 13; table 1 page 18; table 4 --- -/--	1,3-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2001	13/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 23065 A (BOEHRINGER INGELHEIM PHARMA ;HOCHRAINER DIETER (DE); ZIERENBERG BE) 27 April 2000 (2000-04-27) page 1, line 3 - last line page 2, paragraph 3 page 5, paragraph 4 -page 6, paragraph 1; claim 1; example 3 ---	1,2,9
A	US 4 499 108 A (SEQUEIRA JOEL A ET AL) 12 February 1985 (1985-02-12) column 1, line 5 - line 20; claim 1 ---	1,2,9
T	WO 00 30608 A (BRAMBILLA GAETANO ;LEWIS DAVID (IT); VENTURA PAOLO (IT); GANDERTON) 2 June 2000 (2000-06-02) cited in the application page 1, paragraph 1 page 2, line 7 - line 18 page 2, last paragraph -page 3, paragraph 1 page 4, last paragraph -page 5, last paragraph page 7, line 12 - line 25 page 8, line 26 - line 28 page 9, line 8 - line 12 page 9, line 27 -page 10, line 5; claims; examples 1,3-7 ---	1-11
A	WO 96 32099 A (GLAXO WELLCOME INC ;ASHURST IAN C (US); HERMAN CRAIG S (US); LI LI) 17 October 1996 (1996-10-17) page 2, line 12 - line 32 page 3, line 16 - line 25 page 5, line 6 - line 28 page 6, line 5 - line 19; claims 1,2,11,14-17; examples -----	10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-8 relate to a product which has only been defined by reference to an "amino-type drug". The term "amino-type drug" as used in the present independent claim 1 and in dependent claims 2-8 defines the product by a chemical group. However, a product cannot be sufficiently characterised by a chemical group as is done by an expression like "amino-type drug", because it is impossible to know which compositions are encompassed in this expression.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product only by reference to the expression "amino type drug". Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products mentioned in claim 9, and those prepared in examples 1, 2, 4 and 5, and the concept of " amino-type drug".

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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Int ɔnal Application No
PCT/EP 00/04635

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